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Applications of machine learning to diagnosis and treatment of neurodegenerative diseases

Monika A. Myszczynska[1], Poojitha N. Ojamies[2], Alix M. B. Lacoste[3], Daniel Neil[2], Amir Saffari[2], Richard Mead[1], Guillaume M. Hautbergue[1], Joanna D. Holbrook[2] and Laura Ferraiuolo[1] ✉

Abstract | Globally, there is a huge unmet medical need for effective treatments for neurodegenerative diseases. The complexity of the molecular mechanisms underlying neuronal degeneration and the heterogeneity of the patient population present massive challenges to the development of early diagnostic tools and effective treatments for these diseases. Machine learning, a subfield of artificial intelligence, is enabling scientists, clinicians and patients to address some of these challenges. In this Review, we discuss how machine learning can aid early diagnosis and interpretation of medical images as well as the discovery and development of new therapies. A unifying theme of the different applications of machine learning is the integration of multiple high-dimensional sources of data, which all provide a different view on disease, and the automated derivation of actionable insights.

Omics
A collective term for a field within biological research concerned with the study of 'omes'; for example, the genome, transcriptome or proteome.

First described in 1955 by John McCarthy as "the science and engineering of making intelligent machines"[1], artificial intelligence (AI) is a field of computer science research devoted to designing software capable of performing computations with a sophistication similar to that of human intelligence. AI encompasses a wide range of computational systems and tools that mimic actions that the human brain performs on a daily basis: problem solving, reasoning, pattern spotting and knowledge acquisition[2]. Machine learning and natural language processing are the forms of AI most commonly used in health-care settings as they enable a robust interrogation of datasets in order to identify previously undiscovered patterns and relationships between different features in the data[3]. These two forms of AI are distinct, but share common features, as natural language processing largely uses machine learning to derive meaning from language. The functions of machine learning could aid diagnosis, development of novel therapies, and help improve our understanding of the disease course.

The application of machine learning algorithms to medicine and scientific research has been widely discussed in recent years[4–9]. In the last decade, new technologies have enabled rapid accumulation of patient data such as ultrasonography and MRI readouts; omics profiles of biological samples; electronically captured clinical, behavioural and activity data; and social media-derived information[10–13]. These big health datasets are high-dimensional, meaning the number of features (or variables) recorded per observation can sometimes exceed the total number of observations. For example, gene expression datasets can contain the expression levels of ~20,000 genes, whereas obtaining data from 20,000 individuals with a given disease would be extremely challenging. These high-dimensional datasets are often sparse, noisy, cross-sectional and lack statistical power, making it extremely difficult to gain biological insights from these data using traditional data analytical approaches, which look for changes in single variables or perform simple correlations[14]. These problems with data analysis are further compounded by the integration of diverse data types (for example, imaging, genomics and clinical data) that is necessary to gain an understanding of disease mechanisms. In response to these challenges, advanced machine learning models are increasingly applied to biomedical and health-care data. Traditional computer science derives results from input data through the application of predefined rules, whereas machine learning learns rules and insights from input data directly, thus allowing the application of those rules to make predictions from data in new situations. Machine learning approaches can help overcome the challenge of high-dimensional data by reducing the number of features analysed in favour of the least variable[15]. Different machine learning algorithms can also be used to integrate data from different sources to increase statistical power.

By the year 2050, an estimated 22% of the global population will be over 60 years of age[16]. As age is the main

[1]*Sheffield Institute of Translational Neuroscience, University of Sheffield, Sheffield, UK.*
[2]*BenevolentAI, London, UK.*
[3]*BenevolentAI, Brooklyn, NY, USA.*
✉*e-mail: l.ferraiuolo@sheffield.ac.uk*

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Key points

- Machine learning and natural language processing are forms of artificial intelligence that enable robust interrogation of multiple datasets to identify previously undiscovered patterns and relationships in the data.
- Machine learning approaches have been applied to the study of neurodegenerative diseases and show promise in the areas of early diagnosis, prognosis and development of new therapies.
- A substantial number of machine learning algorithms exist, and choosing the correct algorithm to apply to different types of data is crucial to obtain reliable results.
- Neuroimaging was the first area of neurology to benefit from the application of machine learning approaches to improve diagnosis; more recently, application of machine learning methods to motor function and language feature analysis has shown promise in decreasing the time taken to perform clinical assessments.
- The application of machine learning to longitudinal patient data collection and electronic health records has the potential to inform prognosis prediction and patient stratification.
- Large collections of curated datasets and robust assessment of machine learning methods will be needed to achieve full integration of machine learning into diagnostic and prognostic neurology practice and the design of future therapeutics.

risk factor for most neurodegenerative disorders, including Alzheimer disease (AD), Parkinson disease (PD) and motor neuron disease (MND), countries across the world are facing an unprecedented economic challenge[17]. In 2016 the global cost of caring for individuals with AD reached an estimated US$946 billion, which was triple the estimated expenditure in the year 2000 (REF.[16]). These costs are expected to rise, as the number of individuals with AD is likely to reach 115 million worldwide by 2050 (REF.[16]). These estimates call for changes in the way that individuals are diagnosed and treated, and highlight the urgent need for effective therapeutic interventions. In this context, machine learning could enable data to be used more efficiently to provide insights into disease mechanisms, and to help with earlier diagnosis, prognosis, patient stratification and development of new therapies. With these goals in mind, many researchers have gathered rich, high-dimensional datasets from healthy individuals and individuals with neurodegenerative diseases; for example, the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Allen Brain Atlas and the UK Biobank. In this Review, we highlight the latest developments in the use of machine learning to interrogate neurodegenerative disease-related datasets, including the applications of machine learning to diagnosis, prognosis and development of new therapies.

Machine learning models

Machine learning methods are broadly categorized into supervised, unsupervised and reinforcement learning approaches[18] (FIG. 1). Supervised machine learning algorithms are currently the methods most commonly applied to neurodegenerative disease-related data and require a labelled dataset from which to learn. Often, these labels require manual curation or expert assessment; for example, a radiologist is needed to label a set of MRI scan images and a neuropathologist is required to categorize a set of images obtained from post-mortem patient samples. Once this 'benchmark' dataset has been labelled, the machine learning algorithm builds a model of the relationship between the input features (for example, the size of a brain region on an MRI scan) and the label (for example, a diagnostic category). The algorithm can then apply this model to new, unlabelled datasets to predict the label on the basis of the new input features. Gathering sufficiently large volumes of accurate labels for supervised machine learning can be a challenge[19].

Supervised machine learning is divided into classification and regression algorithms[18]. Classification algorithms, such as the example above, predict the categorical output (diagnostic category) for each data sample (patient). In contrast, regression algorithms predict a real-valued variable (for example, degree of functional impairment measured on a continuous scale) for each data sample. When applied to health-care data, both classification and regression algorithms can define patient endotypes by identifying patterns within the data and clustering areas of similarity together. A practical example of regression approaches would be the subtyping of patients into progression endotypes on the basis of algorithms that model motor function decline, disease duration, or slope of progression to form nuanced representations of the progression time series. This regression approach contrasts with endotyping on the basis of categories, which might include specific genetic mutations or the site of disease onset. Most machine learning algorithms have variants to support both classification and regression.

In contrast to supervised machine learning, unsupervised machine learning algorithms do not require labelled data and are useful for tasks such as clustering data samples into groups, or reducing the dimensionality of datasets by generating a simpler representation of highly complex data[20,21]. For example, unsupervised clustering algorithms can be used to analyse gene expression datasets and identify clusters of patients with shared molecular signatures[22]. Furthermore, unsupervised clustering approaches, such as latent variable models, can help identify co-expression modules of genes, which are sets of genes that are likely to be co-regulated or correspond to common biological mechanisms or pathways. In addition to analysing existing data, unsupervised clustering algorithms can also be used to make predictions; for example, a model can be trained on a set of historical clinical data to then predict survival from the cluster that a patient is placed in.

Supervised and unsupervised learning approaches can be combined, for example, to form semi-supervised learning methods[23]. Semi-supervised methods enrich a small set of labelled data with additional unlabelled data, which allows clustering (unsupervised) methods to improve the performance of classification (supervised) methods, as well as regularising the predictive model with additional data. Similarly, transductive learning methods use the test data as unlabelled data to improve a standard supervised classification approach[24,25]; these methods do not result in data leakage as the labels are not shared, and can increase performance in problems where low volumes of data are available.

Finally, in reinforcement learning approaches[26] a reward or punishment is given to achieve a desired output. For example, an algorithm might be used to explore

Endotypes
Clusters of individuals within a disease population that share functional and pathological traits.

Molecular signatures
A collection of proteins, genes and their variants that can be used as hallmarks for a given phenotype.

Regularizing
The technique of adding constraints or knowledge within the training process in order to prevent overfitting.

Data leakage
An undesirable process whereby information is accidentally shared between the training data and the test data, resulting in test evaluation scores that are not representative of real-world unseen data.

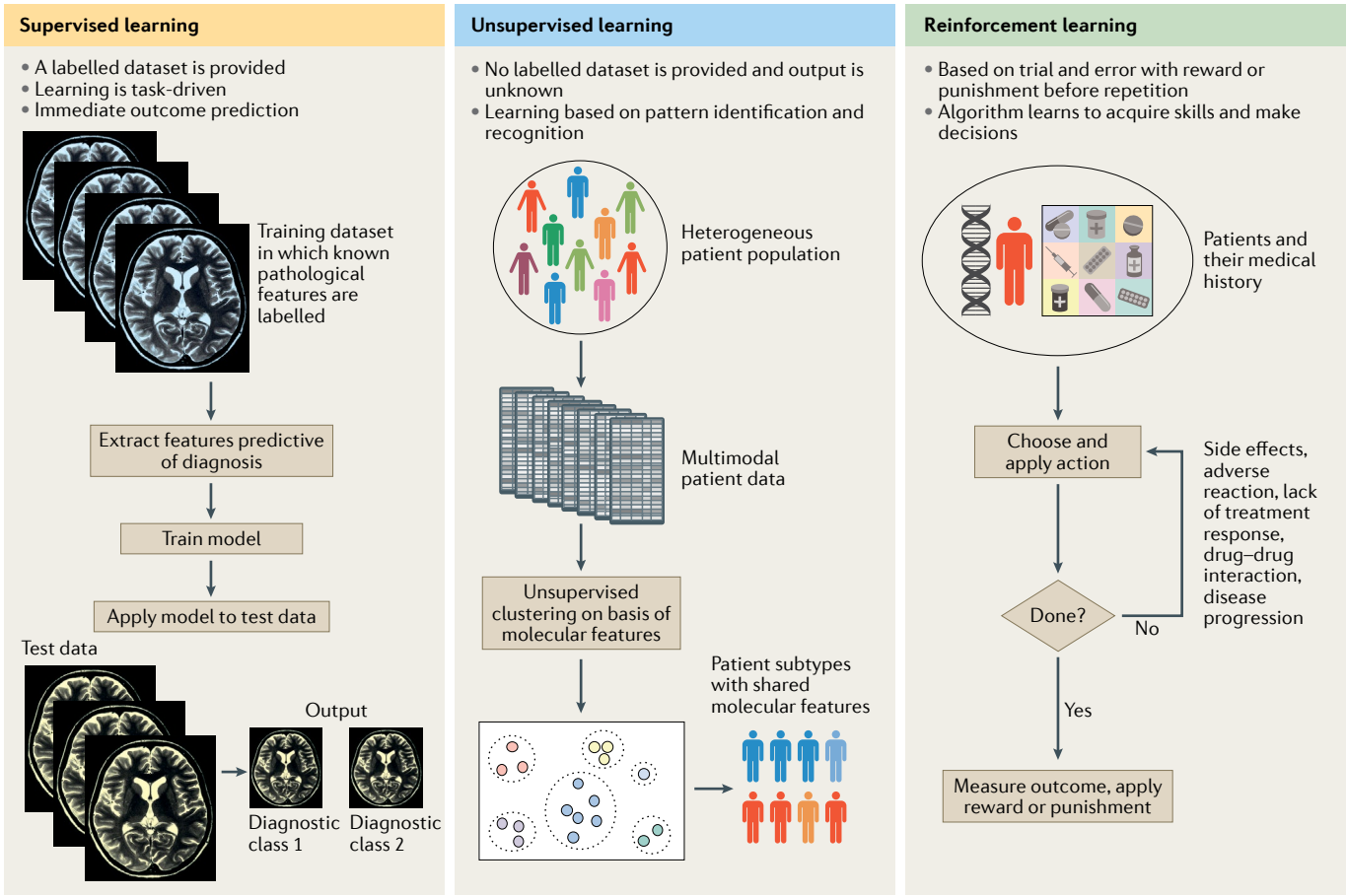


Fig. 1 | **Categories of machine learning.** Machine learning methods can be divided into three main categories: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning relies on a set of data labelled by a professional to train an algorithm to extract specific disease features. Once trained, the model identifies features of interest in unlabelled datasets to aid diagnosis. Unsupervised learning learns to determine patterns and classes within the dataset without labels, and can be particularly useful in identifying molecular signatures that categorize heterogeneous patient disease groups into molecular subtypes. Reinforcement learning models the process of decision making and the output is a result of knowledge gained from previous experiences. The algorithm is trained on a trial and error basis, with a reward or punishment driving the learning process and skills acquisition. Such an approach is ideal for automation and robotics, though use in medicine is increasing. Brain scan image credit: M. Andritoiu/Alamy Stock Photos.

a new medication regimen for a patient based on the patient's medical history. During training, in the event of a negative reaction to a new drug or adverse drug–drug interactions, a punishment would be given to the algorithm, whereas a reward would be given for a drug improving the disease course, which is the desired output. These approaches are being rapidly explored[27,28], but are not yet as widely used as supervised and unsupervised learning in the field of neurodegenerative diseases

Model selection

A substantial number of machine learning algorithms exist and choosing the correct algorithm to apply to a particular type of data is important. With a particular focus on supervised learning, two factors are particularly relevant for selecting the right algorithm: modality (the form that the data is in) and volume (the number of data samples). In terms of volume, for datasets with a low sample-to-feature ratio[29] (SFR <10:1), an algorithm will struggle to learn a useful 'featurization' in addition to classification (FIG. 2). Data featurization requires the algorithm to identify and extract characteristics or 'features' in the data that enable the subsequent separation of data points into classes. The higher the SFR, the easier it will be for the algorithm to identify features that separate the data points. For example, given the limited availability of post-mortem tissue samples for certain neurodegenerative conditions, a model that needs a high SFR to make meaningful predictions about the data, such as a deep neural network, is unlikely to be able to learn from tens of samples and identify features that can accurately classify patients into different pathological subtypes. For such limited datasets, highly constrained or 'regularized' models, such as hierarchical Bayesian models, simplify the task and guide the algorithm by learning only a few parameters for that data.

For larger datasets, support vector machines (SVM)[30] or random forests[31,32] (TABLE 1) are typically used. These approaches are more flexible than hierarchical Bayesian models, but require a greater volume of data and are more complex. SVMs map datasets into a space such that two categories (for example, healthy and diseased)

Sample-to-feature ratio (SFR). The number of data points divided by the number of features; for example, gene expression data comprising tens of patients with thousands of gene expression levels would have an SFR of <1.

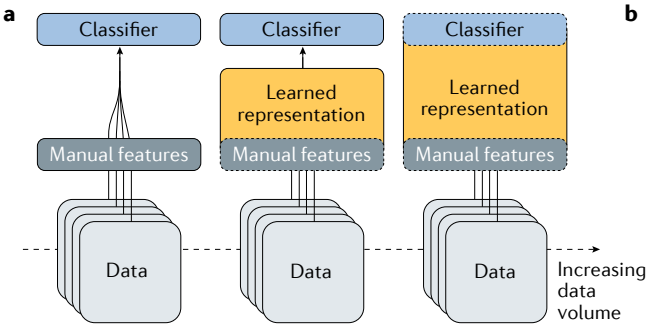
Overfitting
When an algorithm learns the patterns within the training dataset as opposed to the rules representative of the whole class of problems.

Classifier
A type of model used to identify the correct category for a data point.

are separated as widely as possible. In the 1990s, pioneer work demonstrated that the mathematical theory behind SVM, initially used for two-group classification problems, could be applied to more complex and multiclass datasets[33]. Random forests use a different approach to SVM. A random forest algorithm constructs numerous different, independent decision trees, which each require a series of binary choices to be made about the data. In this way, each decision tree provides a classification for the input data, and the algorithm then selects the most common output prediction from the different trees. This approach corrects for the overfitting that can occur when using a single decision tree. SVM and random forests were dominant until the more recent development of neural networks.

Artificial neural networks, which include the popular deep neural networks, are widely used to analyse many modalities of data, but particularly image, video and sound data[19,34] (TABLE 1). These networks are designed to simulate the highly connected neural system found in the brain, and are based on the pioneering work of McCulloch and Pitts[35] who developed a mathematical model to help bridge the gap between statistics and neuropsychiatry. Similar to a neuron receiving electrical stimuli from other neurons, a node in an artificial neural network receives inputs from other nodes. Just as a neuron needs to reach a certain threshold to fire an action potential, the nodes of an artificial neural network sum up the inputs from other nodes and calculate the likelihood that a potential output is true. Artificial neural networks are typically arranged into one or more layers of parallel 'neurons' that transform their inputs into outputs; networks that contain two or more layers are known as deep neural networks. In each successive layer, the neural network is able to manipulate more abstract representations of the data. Artificial neural networks require even fewer manual data manipulation steps during preprocessing than SVM or random forests and in some cases subsume the choice of classifier into the architecture of the network[19]. These networks are mostly supervised, but can also be unsupervised.

The use of a particular type of deep neural network, known as a convolutional neural network (CNN)[36–38] (TABLE 1), has led to significant improvements in machine learning performance for medical image interpretation. CNN, which draws inspiration from the human visual system, extracts features at higher and higher levels of abstraction, initially combining local information and eventually integrating large-scale information across the image. This approach enables complex processing, such as distinguishing cats from dogs or the identification of cancerous cells[39]. Many of the problems involved in



c

Data category	Suggested machine learning models	Example usage in neurodegenerative disorders
Natural language	Specialized natural language processing tools, for example, BERT[153], SpaCy[155], CoreNLP[154] and SyntaxNet[156]	Diagnosis of Alzheimer disease from language data[132]; prediction of linguistic decline caused by dementia[158]
Imaging and volumetric data	2D and 3D convolutional neural networks[19,70]	Alzheimer disease diagnosis[72]
Time-series data	3D and 4D convolutional neural networks[122]	Parkinson disease diagnosis from wearable device that measures gait[119]; activity recognition[126]
Graph data	Graph convolutional neural networks[178]	Prediction of drug adverse effects[176]; molecular fingerprint prediction[177]
General data and multimodal data	Hierarchical Bayesian models[83]; support vector machines[76]; random forests[32]; variational autoencoders[73]	Dementia classification[76]; ALS progression prediction[32]

Fig. 2 | **Determining the best machine learning model for a given problem.** Two factors are particularly relevant to the choice of machine learning model: the data modality (for example, time series or imaging) and the data volume (number of data points). **a**,**b** | At small data volumes, manual features and well-regularized classifiers are needed. As data volume increases, a learned representation that discovers features from data automatically can be used, and eventually a separate, custom classifier on the learned representation is no longer needed. **c** | Choosing the right model to match the data type enables machine learning to extract a meaningful representation from the data, which can be paired with a variety of classifiers. ALS, amyotrophic lateral sclerosis; BERT, Bidirectional Encoder Representations from Transformers; SVMs, support vector machines.

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Table 1 | **Descriptions of key machine learning methods and examples of their application**

Method	Supervised or unsupervised?	Classification, regression or clustering?	Definition	Examples of application
Deep neural networks	Supervised and unsupervised	Classification, regression, and clustering	A category of algorithms that are composed of multiple layers of transformation, and use artificial neural networks as each layer of processing	Disease diagnosis from neuroimages, speech recognition, natural language processing and pattern recognition[19,71]
Convolutional neural network	Supervised and unsupervised	Classification, regression and clustering	Form of a deep neural network designed to mimic neuronal connections and reduce dimensionality of the data	Image analysis and classification, video analysis, natural language processing and acoustic input[65,92,93,158]
Recurrent neural networks	Supervised and unsupervised	Classification, regression and clustering	A type of artificial neural network capable of forming internal memory, which makes it optimal for analyses of sequential data	Speech classification, handwriting classification and disease progression classification[92,140]
Network diffusion algorithm	Unsupervised	NA	A class of methods that model the spread of information through networks	Gene regulator analysis and network inference for gene prioritization[149]
Random forest	Primarily supervised	Primarily classification and regression	An algorithm that averages a large number of weak classifiers (trees) to form a strong classifier using random subsets of data	Disease progress prediction[32]
Support vector machines	Primarily supervised	Classification, regression and clustering	A method of separating distinct classes within a dataset by applying an optimal hyperplane	Disease classification[54,58–60,82,210]

NA, not applicable.

image classification can be solved by these kinds of algorithms. Another type of deep neural network, known as a recurrent neural network (RNN)[40] (TABLE 1), can extract information from sequences of data and is particularly useful for analysing clinical records. RNN models such as long short-term memory (LSTM)[41] and gated recurrent units[42] form building blocks used in most sequence tasks. These models contain a memory cell that allows the algorithms to learn long-term dependencies and gates that control the exposure of the memory content and the extent of the changes made to the memory content depending on the input.

Some of the key technical risks to mitigate when choosing a machine learning model include insufficient data volume, improper data representations, overfitting, incorrect hyperparameter selection and missing data[43,44]. Although subject matter expertise can help address issues regarding data volume and data representation, overfitting is a fundamental issue. For example, when a model is trained on a dataset with low bias and high variance, and the model selected has the best performance on the training data, the model is likely to try to 'memorize' the training data. This memorization results in overfitting of the model on the training data, leading to poor predictive performance on test data as the model is no longer able to make generalizations to the additional datasets. Overfitting could, for example, lead to some pathological features in neuroimages not being identified. Methods such as cross-validation and regularization can help minimize this problem[45]. All machine learning methods and data sources have caveats; therefore, a combination of multiple data sources and methods followed by confirmatory post-processing steps that use a variety of metadata is the best approach.

Hyperparameter
A parameter the value of which is set before training; for example, the attributes of the model architecture.

Cross-validation
A training and evaluation procedure that consist of splitting the data into subsets and alternately holding out one subset for evaluation until all subsets have been evaluated.

Metadata
Data about other data; for example, information about an experimental protocol or the time and date of sample collection.

Diagnosis and prognosis

In many neurodegenerative diseases, including AD, PD and MND, symptoms do not manifest until a substantial loss of neurons has already occurred[46–48], which makes early diagnosis very challenging. Therefore, research into the application of machine learning models to early diagnosis is growing (TABLE 2). The aim of this research is to use machine learning to detect prognostic signals in data that can be collected relatively easily (for example, electronic health records (EHRs) or MRI data), thus enabling the prospective screening of ageing populations. The machine learning-driven automated diagnosis could then flag individuals for further clinical investigation. Such an approach would require machine learning models that are sensitive enough to detect early disease signals and specific enough not to over-burden health systems with unnecessary follow-up tests. Currently, test results need to be analysed and interpreted by trained staff, which can lead to delays in diagnosis. These delays could be reduced by applying machine learning approaches to the data as they are gathered in the clinic. These same data could be used to predict patient prognosis by comparing disease progression at any given time with historical data from patients sharing the same endotype or phenotype. Historical health records provide a helpful training dataset for prognosis algorithms, as they can cover the entire disease span.

Neuroimaging. Neuroimaging techniques such as CT and MRI are often used in the diagnosis of neurodegenerative diseases, and radiology was one of the first fields to benefit from the computerization of medicine and the introduction of 'intelligent machines'[49] (FIG. 3). The early 1990s saw the introduction of supervised

Table 2 | **Key neurodegenerative disease-related data types used by machine learning algorithms**

Neurodegenerative disease	Key data types used	
	For diagnosis	For monitoring disease progression
Dementias, including AD and MCI	Neuroimaging[30,55,72,75–77,79,82]; cognitive performance tests[131,132,135,136]; EEG data[104]; transcriptomic data[97,140]; biomarker data[143,144,146]	Neuroimaging[77,83,211]; cognitive performance tests[131,132,158]; IADL records[125,126]
PD	Motor performance tests[114,115,119]; neuroimaging[86]	Electronic health records[165]
MS	Metabolomic data[145]; neuroimaging[85]	Genomic data[142]

AD, Alzheimer disease; EEG, electroencephalogram; IADL, instrumental activities of daily living; MCI, mild cognitive impairment; MS, multiple sclerosis; PD, Parkinson disease.

knowledge-based expert systems[50–55], which were capable of recognizing pathological events in the brain on the basis of a large amount of data and knowledge collected by the neuroradiological community[56]. Initial studies used clinically relevant diagnostic features, such as cortical thickness or morphology of particular brain regions, to classify patients and help radiologists make a diagnosis[57–63]. This approach is known as computer-aided diagnosis, and continued to be developed and improved throughout the early 2000s[64–68]. Because machine learning is purely evidence-based and can analyse problems in an unbiased manner, the approach is helpful for making objective diagnoses from medical images and often surpasses the performance of trained professionals in terms of speed, precision and accuracy[30,69].

Computer-aided diagnosis systems can be supplemented with and powered by supervised learning techniques to further improve the interpretation of neuroimaging data and help identify subtle abnormalities in the images that are not detected by radiologists. For example, CNNs can categorize images by identifying and mapping a high number of features[70] (TABLE 1). Some studies have used CNNs to predict a diagnosis of AD[71,72] and to study cognitive ageing[73] from MRI and PET images, sometimes alongside other clinical readouts (for example, biomarker information and assessments of motor or cognitive performance), to increase specificity.

SVMs have been used to analyse MRI data, sometimes combining structural and functional MRI, and cognitive assessment data to improve disease diagnosis[74] (TABLE 1). For example, one study used an SVM to differentiate between structural MR scans from individuals with different severities of AD and cognitively normal elderly individuals, as well as to differentiate between individuals with AD and individuals with frontotemporal lobar dementia (FTLD)[75]. In another study of structural MRI data, an SVM was able to predict conversion from mild cognitive impairment (MCI) to AD, as well as separate healthy controls, individuals with MCI and individuals with AD better than a combination of statistical approaches and expert knowledge[76]. In the same year, a study used a combination of linear dynamic system and SVM algorithms to integrate MRI data and cognitive test data to distinguish individuals with AD from healthy controls[77]. This study is particularly interesting because of the use of two approaches to integrate data. SVMs have also been applied to whole-brain anatomical MRI images to identify new regions of interest that can differentiate between individuals with AD and healthy controls[78], and to images of the hippocampus to classify its shape features[79]. The latter method has been described as more accurate than traditional hippocampal volumetry[80,81]. An SVM was also used to compare the utility of different combinations of neuroimaging data (functional MRI or structural MRI) and cognitive performance data for identifying individuals with MCI[82]. Analysis of MRI data with SVM has also been used in studies of cognitive function[83], stroke[84], multiple sclerosis (MS)[85] and parkinsonism[86].

MRI produces images of higher resolution than CT; however, the diagnostic performance of CT can be improved with the use of machine learning algorithms. For example, in one study, a random forest algorithm for automated white matter lesion detection was applied to a set of CT images from individuals with acute ischaemic stroke and performed similarly to the labelling of MR images by radiologists[87]. The algorithm had a failure rate of 4% and an average processing time of less than 2 minutes, thus offering a possibility of similar approaches being extended to diagnosis of neurodegenerative diseases. Machine learning can assess images quickly, so it could be used to flag findings from CT images that need urgent review by a radiologist in life-threatening scenarios[88–90]. Quick image analysis could also be extended to MRI, which could prove particularly useful for individuals with MCI[91–93], as early prediction of possible conversion of MCI to AD could enable a swifter start of treatment.

In a global effort to improve our understanding of neurodegenerative diseases and their progression, databases of neuroimaging data from patients are being assembled with the aim of creating a comprehensive picture of the disease course from diagnosis onwards. Resources such as the Parkinson's Progression Markers Initiative, ADNI, The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[94] or European Alzheimer's Disease Consortium Impact of Cholinergic Treatment Use (EADC-ICTUS) give researchers working with machine learning algorithms access to verified material to be used for algorithm training and validation. Although the training data are becoming widely available, applying algorithms to it can be challenging. Some pieces of software are not, or were not for a long time, capable of reading and processing the DICOM file format that is used for medical imaging. However, open source software and libraries with a strong user community, such as Google TensorFlow have now addressed this issue by extending support to additional file formats, including DICOM[95].

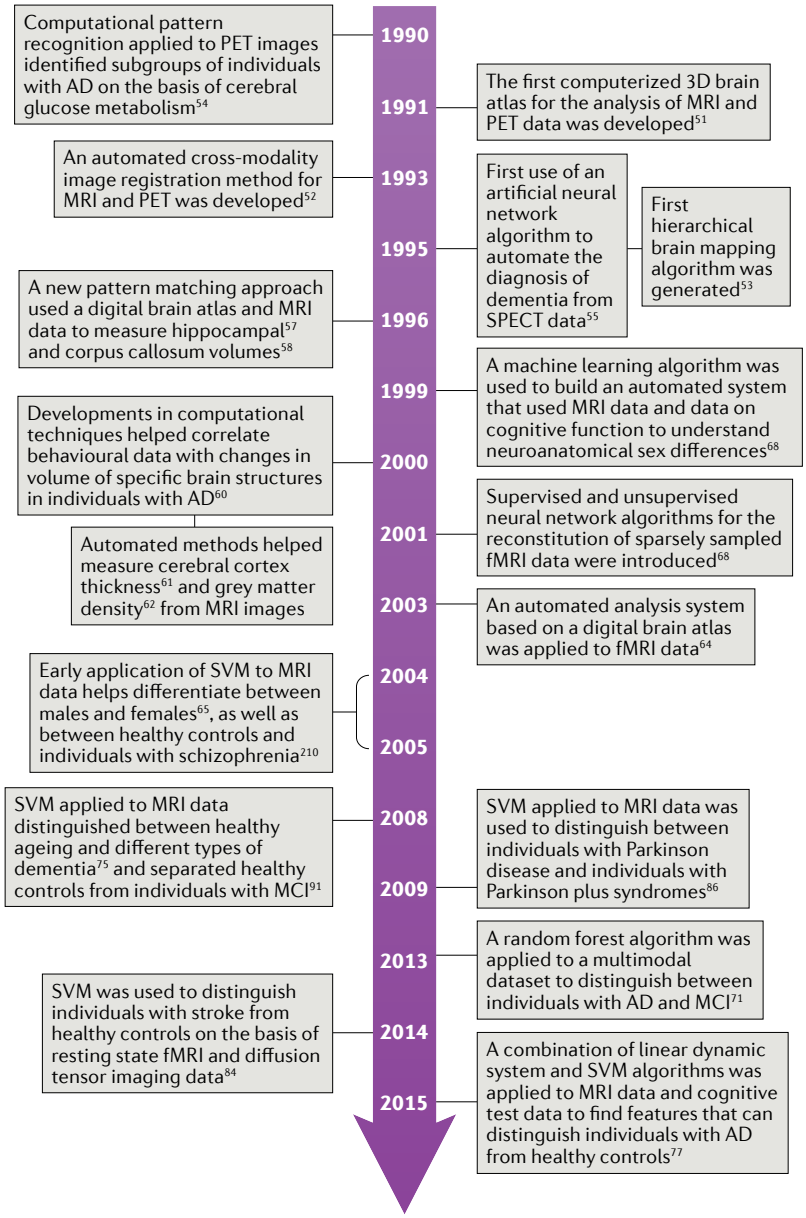

Fig. 3 | **Key developments and novel applications of computational and machine learning techniques to neuroimaging since the 1990s.** Interest in machine learning and its use for medical purposes towards the end of the 20th century led to the automation of previously time-consuming manual analysis and measurement of neuroimaging data. The low variance and high reproducibility of these AI-driven methods made them an attractive tool for use in clinical settings. Moreover, three-dimensional, high-resolution overview of deep brain structures, previously considered to be beyond analysis without surgical interventions, became within reach. AD, Alzheimer disease; fMRI, functional MRI; MCI, mild cognitive impairment; SPECT, single-photon emission computerized tomography; SVM, support vector machine.

Efforts to investigate the interaction between genetics and brain structure have led to the rise of a new field called neuroimaging genomics[96]. The very first attempts to draw a correlation between genetics and brain function were initiated in the early 2000s and focused on single gene variants[97,98]. These pioneer studies made several novel observations, including the association of the epsilon 4 allele of the apolipoprotein E gene (*APOE* ε4) with abnormalities in brain activation assessed with functional MRI during memory-activation tasks[99]. Since these initial studies, the field has generated breakthroughs owing to large multicentre collaborations such as the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) Consortium, which has analysed genome-wide association study (GWAS) and MRI data from 30,717 individuals across 50 cohorts[100]. The ENIGMA Consortium has now identified common genetic variants that influence the volume of several brain structures, thus shedding light on potential complex genetic drivers of development and disease. As ENIGMA expands, specialized working groups dedicated to the study of several disorders, including PD, ataxia and FTLD, have been formed to help elucidate the pathogenesis of these diseases using imaging genomics.

Neuroimaging is one way of investigating brain activity. Other methods of monitoring brain activity, such as electroencephalography (EEG), can also benefit from machine learning-driven data analyses. EEG data have been used to distinguish individuals with AD from healthy controls[101] or patients affected by other forms of dementia[102], as well as to detect functional changes in dopaminergic neurons to diagnose PD[103]. In order to do this, changes in electrical activity frequency over time in different areas of the brain are analysed. Algorithms based on artificial neural networks have been generated to differentiate between individuals with AD and individuals with MCI using only unprocessed EEG data, with the aim of speeding up diagnosis and simplifying the monitoring of dementia progression[104].

Motor function. Many neurodegenerative disorders, such as MND, Huntington disease (HD) and PD, are characterized by motor dysfunction, often culminating in loss of movement[105,106]. An understanding of the progression and chronology of motor degeneration is essential for supporting patients appropriately at each stage of the disease. Motor performance is measured during routine clinical assessments, which often assess both fine and gross muscle functions (for example, muscle tone when picking up small objects and gait when walking), although the precise battery of tests varies depending on the disorder[107–109].

Machine learning can be used to assess the performance of individuals in complex tasks, such as drawing, in a time-efficient manner[110]. Simple drawing tasks and handwriting analysis are being increasingly used in the early diagnosis of PD[111,112], as handwriting is no longer an automated function in individuals with the disease and is performed in a more segmented and sequential manner, with numerous pauses[113]. Introduction of machine learning techniques into writing task analysis can help classify individuals with PD and serve as a diagnostic tool. In one study, classifier-based supervised machine learning algorithms were applied to data from a horizontal line drawing task in order to differentiate between normal and abnormal hand movements and identify irregularities characteristic of PD[114]. A set of metrics related to the velocity and spatiotemporal trace of the pen combined with naive Bayes classification helped to accurately distinguish between individuals with PD and healthy controls. Similarly, in another study, a supervised model was

Genome-wide association study
(GWAS). An observational method of studying genetic variants across a population in search for associations between genetic changes and traits such as diseases.

used to automatically analyse Archimedean spiral tracing performed by individuals with PD[115]. Drawings were independently assessed and scored by trained experts, and the algorithm-scored drawings showed comparable results. The drawing tests were performed on patients' personal computers and the software support for such tests can be extended to commercially available smartphone or tablet set-ups, making it an easily obtainable and cost-effective approach to motor function analysis.

Machine learning-based hardware such as the Parkinson's KinetiGraph[116] and the Kinesia system[117] are designed to score motor function, dyskinesia and bradykinesia in individuals with PD, and are widely available. The Parkinson's KinetiGraph can be worn on a wrist and measures wrist acceleration. The Kinesia system is worn on either a finger or a wrist and detects motion with an in-built accelerometer and gyroscope. Both systems provide automatic scoring of an individual's motor symptoms, but the output data can also be analysed further using machine learning algorithms, such as SVM. For example, a recent study classified PD tremor severity using the Kinesia system's recordings[118]. Gait analysis algorithms also show a lot of promise in early diagnosis of motor disorders. For example, an RNN and LSTM were used to classify a database of gait analysis recordings, such as measures of stride-to-stride footfall times, and distinguished healthy controls from individuals with PD, HD or MND with an accuracy of 95–100%[119]. Moreover, the two algorithms in combination performed better than an SVM alone[120], suggesting that existing algorithms could be further improved to optimize performance.

Data on movement can also be useful in the study of AD. Film footage of patients performing instrumental activities of daily living (IADL) (for example, bathing, dressing and eating) can be watched and manually scored by clinicians[121]. However, this approach can be time-consuming and automating this process would be of major benefit to neurologists investigating IADL. Deep learning and CNN-based machine learning algorithms are capable of recognizing action from video footage[122] and this technology has been applied to action recognition in IADL recordings[123]. However, the use of cameras to monitor IADL has implications for patient privacy[124]. New technologies such as the random forest algorithm-powered SmartFABER solve privacy issues by collecting data from motion and contact sensors placed around the home, feeding this data back to software installed on the individual's local personal computer, and analysing user movement and interactions with objects[125]. Data from wearable sensors has also been used for machine learning-based activity recognition. For example, one study found that LSTM algorithms performed better than standard CNN approaches in activity identification and classification from this kind of data[126]. In contrast to the Kinesia system or Parkinson's KinetiGraph, the sensors used to generate the data used in this analysis were worn on multiple parts of the body, which enabled the study of complex movements, such as using a toggle switch, cleaning a table, opening and closing doors and drawers. Although individuals with PD currently stand to benefit the most from wearable technology, smartwatch-based wearable sensors that use SVM for recognition of agitated behaviour in individuals with dementia show promise[127].

Language features. Language features are important indicators of cognitive state, as communication skills and interpersonal behaviour deteriorate in many neurodegenerative diseases[128–130]. Machine learning approaches have been used to extract language features from audio recording transcripts in order to distinguish between individuals with AD and healthy individuals. For example, the authors of one study analysed the way patients compose verbal utterances and used the resulting lexical features to differentiate between individuals with AD, MCI or vascular dementia and healthy controls[131]. Several different algorithms were tested, out of which the SVM performed most consistently. In another study, an n-gram language model was used to analyse the vocabulary of participants and the frequencies with which they used specific words together in a sequence[132]. The algorithm assigned a perplexity score to the utterances, meaning that the higher the perplexity score, the more unforeseen and convoluted the utterance, and the more likely the individual was to have an AD diagnosis. In individuals with AD, the perplexity scores were found to correlate with mini-mental state examination scores, thus showing the potential of this approach as a diagnostic tool.

In addition to the machine learning-based analysis of transcripts, AI-driven interactive avatars have been used to capture more complex language data. Inspired by early interactive computers[133], avatars are animated humans that ask the patient pre-programmed questions and record the resulting conversation[134]. Avatars most often take the form of software installed on the patient's personal computer or tablet and no time limit is applied to patients' responses, which is a scenario that is difficult re-create in face-to-face clinical visits. In one example of the use of an avatar[135], a set of questions based on clinical examination tools (mini-mental state examination, objective structural mental examination and the Wechsler memory scale-revise test) was used to assess participants for symptoms of dementia. In this study, SVM and logistic regression were used to assign a diagnostic category to patients on the basis of speech features and audiovisual cues extracted from the video recordings (for example, smiling, eye contact and consistent delays in answering the questions). This approach was able to distinguish between healthy individuals and individuals with dementia with an accuracy of 93%[135]. This study highlights a key benefit of using avatars over the traditional analysis of transcripts, as allowing patients to speak freely and naturally enables the recognition of new speech features, such as pitch and tone changes or breathiness. Transcripts of conversation would not take such features into account and are limited by patient–doctor contact time constraints. A similar AI system was used as a conversation analysis aid in a memory clinic and identified four out of six participants with neurodegenerative dementia and six out of seven participants with functional memory disorders[136], which are important in the differential diagnosis of prodromal

dementia[137]. As the number of individuals with suspected dementia is rising[17], installation of avatar software on an individual's personal computer could enable the evaluation of speech features at home, which would help speed up diagnosis, save medical personnel time, and reduce the fatigue and potential distress caused by the need to travel to a memory clinic[136]. Speech data are complex and contain a large number of different features. Therefore, deep neural networks[19] (TABLE 1) are frequently used to perform pattern recognition in this kind of multilayered data.

Molecular and genetic data. Improving our understanding of the molecular foundations of neurodegenerative disorders is key for the development of new therapies and for diagnosis and prognosis. Next-generation sequencing techniques have increased the speed of DNA sequencing, enabling large volumes of data to be acquired relatively quickly. The volume of genomic data produced, especially in GWAS and other large cohort studies, requires a well-refined analysis approach and machine learning techniques are proving useful in this area. Multiple AD-associated genes have been identified[138], but the idiopathic nature of the disease, along with its high heritability, suggests that further genetic risk factors or complex genetic interactions might play important roles in disease onset or progression[139]. GWAS aim to unravel some of these complex relationships. For example, in one study a supervised SVM-based algorithm was used to interrogate brain-specific gene expression data with the aim of identifying novel AD-associated genes[140]. The authors used a training dataset of 335 AD-associated genes identified through previous GWAS and other genetic studies and 335 non-AD-associated genes, and integrated brain-specific gene expression data to train the classifier to identify AD-associated pathways. The authors then used the trained algorithm to identify genes that interacted closely with the known AD-associated genes in the brain-specific network and ranked these new candidate genes by AD association probability. The top candidates corresponded to genes previously identified as AD-associated by GWAS, but the authors also identified a number of genes involved in cellular processes, such as enzyme binding, that had not been identified before.

A different approach was taken in another study, in which gene expression profiles were predicted from ADNI GWAS data and a range of different machine learning algorithms used to identify associations between AD diagnosis and gene expression profiles across different tissues[141]. In this study, the RNN was the most accurate algorithm for distinguishing individuals with AD from healthy individuals. The authors also tested the performance of the algorithm in predicting disease phenotype, but the results were inconclusive, probably owing to the complexity of the interaction between genetics and environment. Using machine learning to cluster patients based on their genomic similarity is also helping to develop stratification tools for MS[142], the hope is that this stratification will help triage patients after diagnosis and predict their individual disease trajectory.

Applying machine learning to study protein signatures in samples from patients can aid biomarker discovery, which in turn is likely to improve disease diagnosis. In a study by Ray et al.[143], published in 2007, a classification algorithm called predictive analysis of microarrays was used to identify plasma proteins that could discriminate between individuals with AD and healthy individuals when given a cohort of blinded samples. Starting from a pool of 120 proteins assessed using an enzyme-linked immunosorbent assay, the authors identified 18 signalling proteins, the blood expression level of which was used to distinguish between samples from individuals with AD and healthy controls with close to 90% accuracy. These 18 proteins were also used to identify patients who had MCI that progressed to AD within 2–6 years of sample collection. Several years later, in a study by Agarwal et al.[144], an unsupervised artificial neural network algorithm for both feature selection and classification was applied to the same dataset as used by Ray et al.[143]. The artificial neural network identified a smaller set of nine proteins, as opposed to 18, that distinguished individuals with AD from healthy controls with accuracy similar to that found by Ray et al., resulting in significant economic savings. Of these nine proteins, seven were common between the two studies, whereas two were new findings. In addition, Agarwal et al.[144] identified a cluster of 29 proteins that identified individuals with MCI that would progress to AD, individuals with MCI that would progress towards other dementias, and individuals with AD. This prediction accuracy could not be achieved with either the nine-protein or the 18-protein clusters identified in the two studies. Comparative studies of this kind highlight how advances in machine learning approaches can refine and improve disease classification and prediction accuracy to benefit patient health, as well as reduce economic costs.

Similarly, in recent studies machine learning has been applied to metabolomics data from individuals with MS[145] or AD[146] to identify new biomarkers for these diseases. In the first study[145], 400 plasma metabolites were assessed in a small cohort of 12 individuals with MS and 13 healthy controls. Supervised random forests, with 5,000 trees and 100 randomly selected metabolites to determine classification at each node in a tree, were applied to identify six metabolites, an increase in the expression of which predicted a diagnosis of MS with a probability of 80%. In another study[146], a similar random forests approach was used to analyse the prediction power of a combination of clinical and biochemical data, including data on metabolomic, genetic, functional health, lifestyle, cognitive and bio-demographic risk markers. The analysis showed that different combinations of the six risk markers resulted in statistically significant discrimination between individuals with AD, individuals with MCI and healthy controls.

Clinical records. In addition to the applications discussed above, machine learning can be used to mine routinely collected health-care data for new insights. EHRs are compiled by health-care providers and contain the medical history of individuals under their care, which can include information on immunizations, prescribed

Next-generation sequencing
High-throughput, deep sequencing of DNA and RNA; this technique utilizes sequencing technologies that are capable of processing multiple DNA or RNA sequences in parallel.

Metabolomics
A study of metabolites, that is the small molecule substrates, intermediates and products of cellular metabolism, and their interactions within living organisms.

medications, test results and vital signs. EHRs are being increasingly implemented worldwide[147,148] and the collection of data in this way requires no additional input from patients[149]. However, EHR data were intended to be read by humans and often consist of unstructured notes written by health professionals. Therefore, EHRs need to be converted into computer-readable formats before being analysed with machine learning techniques. Machine learning-enabled natural language processing techniques focus on methods to process and interpret human language[150–156] (TABLE 1), and can be used to access the information contained within EHRs[157,158]. The current state-of-the-art approach[153] for natural language processing uses deep neural networks pre-trained on billions of words to perform tasks such as predicting missing words in sentences or identifying whether two sentences follow each other. After training, these deep neural networks can be fine-tuned for a variety of tasks, including question answering or inference, in an example of transfer learning. One example of the application of natural language processing to health-care data is the Comprehend Medical initiative by Amazon, which is a service that helps extract meaningful information, such as the presence of a gene mutation, date of symptom onset or identification of pathologies, from unstructured data such as EHRs.

Machine learning can be used to perform time series analyses on longitudinal EHR data. In these analyses, an algorithm learns prognostic signatures from historical data and looks for these signatures in new datasets to create personalized health forecasts for patients. For example, in one study, data from cognitive tests performed regularly at a memory clinic were used to plot the pattern of change associated with cognitive decline. This information, in combination with other clinical information, was applied to data from individuals who were in the early stages of the disease to identify early signs of worsening of dementia[159]. Such an approach might prove particularly useful in diseases characterized by aggressive decline and poor survival such as MND, for which the average survival after diagnosis is 3–5 years[160]. Existing statistical models of MND use data from routine clinical assessments to predict patient prognosis for up to one year[161], and recent improvements to this approach can make personalized predictions for up to 120 months depending on the disease severity[162]. These models, however, do not take into consideration an individual's previous medical history, which could be informative, and missing data can result in biases.

In a study of PD progression, a Bayesian multivariate predictive inference platform was applied to clinical information, including analysis of motor progression assessments as well as complete genetic and molecular data, collected over a 2 year period from a cohort of 117 healthy controls and 312 individuals with PD[163]. A total of 17,499 features were included in the model with the aim of identifying novel predictors of motor progression in the early stages of PD. The progression modelling confirmed some known factors for faster motor decline, such as higher baseline motor score, male sex and older age, but it also identified new predictors, such as genetic variation and cerebrospinal fluid biomarkers.

Deep learning methods rely on the input of large quantities of data and are suited to the analysis of EHRs, which, in some cases, contain information on the majority of a national population. RNN models have been effectively applied to EHRs to predict clinical events and improve diagnosis. For example, one study applied LSTM RNNs to data provided by the US National Alzheimer's Coordinating Center, which includes 12 years of heterogeneous medical information on 5,432 individuals with probable AD. The study aimed to predict the AD progression stage of the next hospital visit by a patient only on the basis of the information of the patient's historical visits. By integrating clinical data, including global staging Clinical Dementia Rating scores and the Functional Activities Questionnaire results, the algorithm could predict a patient's AD progression on the next visit with over 99% accuracy, significantly outperforming classic time series forecasting methods[164]. Similarly, an RNN-based method was used to compare longitudinal health records from different individuals with PD and group these records according to similarity[165]. This kind of approach could be used to identify disease subtypes within a patient population. In another study LSTM was applied to EHR data to predict the length of time that patients affected by different pathologies would stay in hospital[166]. The algorithm performed better than traditional clinical predictive methods across different hospital wards, including neurological units, which is indicative of the versatility of machine learning approaches and shows promise for the application of this method to neurodegeneration.

Ensuring that the private data of individual patients is protected while allowing access to health records for research purposes is an ongoing challenge. In an attempt to address this challenge, machine learning was used to anonymize EHRs from a mental health-care provider and was able to mask 98.8–100% of patient identifiers that appeared in the text — the only errors resulted from misspelling of words in the original record[167].

Therapy development

Effective treatments for many neurodegenerative diseases are lacking, but the high failure rate of clinical trials for these diseases has led to the withdrawal of investment by large pharmaceutical companies[168–171]. For example, over 400 clinical trials of potential treatments for AD were performed between 2002 and 2012, but only one drug, memantine, was approved[172]. Similarly, in the last 20 years, 50 clinical trials of drugs for MND have failed to show positive results. Riluzole and edaravone are the only drugs approved to treat MND and both have demonstrated only a modest improvement in patient survival and functional ability[173]. These unfortunate failures highlight the complexity of developing therapies for brain conditions and create opportunities for new approaches to drug development.

Target identification. Neurodegenerative disorders involve a vast array of mechanisms that all contribute to disease pathology. For example, in MND, multiple processes, such as RNA metabolism, axonal transport, mitochondrial function and autophagy, are implicated

in the degeneration and death of motor neurons[174]. The ability to explore the data related to these pathways in a thorough, holistic and efficient manner is key to understanding disease, but can be challenging for individual scientists. Machine learning can help make sense of this complexity and even predict drug targets.

One machine learning approach to drug target identification is relational inference on a knowledge graph, which links entities such as genes, diseases and drugs. Knowledge graphs are typically built from the integration of multiple data types; for example, data extracted from full text articles on PubMed, and from databases such as KEGG, OmniPath, Ensembl and ChEMBL[175–178]. Knowledge graph approaches can learn non-obvious links between diseases and biological drug targets (for example, identifying a new therapeutic protein target on the basis of its interaction with a protein known to be mutated in a particular disease), and are attractive because a single algorithm can be used to make predictions for multiple diseases. One downside of using these approaches on their own is that they can lack granularity in their biological relationships (for example, context of different brain regions), which can lead to predictions with low specificity. This can be a particular problem in neuroscience, where differences in gene interaction networks between different brain regions might be important to understanding the disease pathophysiology and treatment potential[179]. Several relational inference methods have been published that performed well on a benchmark dataset for a wide range of disorders, including neurodegenerative diseases[180]. However, to date new hypotheses generated using these approaches have not been scientifically validated.

Machine learning can also be used to perform large-scale text mining to suggest proteins that might be related to a disease of interest. In contrast to knowledge graphs, which only take into account relationships between entities, this approach uses the entire text as substrate, thus enabling a more detailed specification of biological context. In one study, an automatic method was used to extract text features from the published literature and create a model of the RNA-binding proteins (RBPs) previously associated with MND[181]. This model was then applied to a candidate list of other RBPs and used a network diffusion algorithm to identify those most similar to the known MND-associated RBPs. Of the ten best candidate RBPs identified by the machine learning analysis, five showed significantly altered levels in individuals with MND when compared with controls, indicating that the model's predictions were accurate.

Machine learning-based analysis of biological samples (for example, post-mortem CNS tissue) might also provide useful information for target identification. Gene expression data from individuals with disease and healthy controls can be used to build molecular networks that visualize the biological processes that are altered in the disease state. For example, a combination of co-regulation, clustering and Bayesian inference was used to analyse transcriptomic data from brain tissue samples from individuals with late-onset AD and controls, and identified groups of genes that were altered in the diseased tissue[182]. A group of immune-related and microglial-specific genes were more highly expressed in individuals with late-onset AD than in control individuals, and the microglial protein TYROBP was identified as a key regulator of this group. Deficiency of this protein was subsequently found to be neuroprotective in a mouse model of AD[183,184], suggesting TYROBP as a new therapeutic target.

Patient stratification. Heterogeneity in clinical manifestation, disease progression and genetic predisposition often exists within groups of individuals diagnosed with the same neurodegenerative disease[185]. This heterogeneity makes it difficult to understand disease mechanisms from studying the diagnostic group as a whole, as different mechanisms could be responsible for the disease in different individuals and makes identifying effective therapies more challenging. Therefore, stratifying study participants according to more detailed criteria than a diagnostic class is becoming more common. The use of machine learning techniques for this purpose is becoming increasingly popular, as the entirety of an individual's clinical history and additional data, including, transcriptomic, neuroimaging or biomarker expression data, can be fed into the algorithm[186]. One approach to patient stratification using deep data might be to use unsupervised machine learning methods to reduce dimensionality in high-dimensional labelled data and derive classifiers of patient outcomes. This approach can identify patients with different subtypes or endotypes of the disease, which would otherwise not have been obvious[187], for further study of disease mechanisms or development of endotype-specific therapeutic strategies (FIG. 4).

Heterogeneity in patient populations is also a problem for clinical trial design. Natural heterogeneity in the outcome variable is an unhelpful source of noise that can mask the effects of a therapeutic intervention. A lack of biomarkers means that clinicians often rely on subjective self-reported clinical measurements for diagnosis and detecting a response to therapeutic intervention[188]. Therefore, using machine learning models to stratify patients and identify biomarkers of treatment response from clinical and molecular data could improve the efficacy of clinical trials. Indeed, patient stratification and biomarker identification are major objectives of large publicly funded databases such as the ADNI. For example, an approach was developed to combine multiple machine learning models that used clinical, cognitive and genetic data collected in an international, multicentre effort, to predict survival in patients with MND[162]. The aim of this model was to provide information that could be used to stratify patients for clinical trials. Another study used a random forest algorithm to predict disease progression in individuals with MND on the basis of 3 months of clinical examination data[32]. Although this model has not yet been used to stratify patients in a clinical trial, seeing patient data-driven models that are predictive of disease outcomes is encouraging.

Conclusions and future challenges

Machine learning algorithms can recognize patterns and make novel inferences from large amounts of multidimensional data in a way that humans cannot. However,

Bayesian inference
A method of statistical inference that uses Bayes' theorem to calculate the probability of a hypothesis being true on the basis of observed data and prior information.

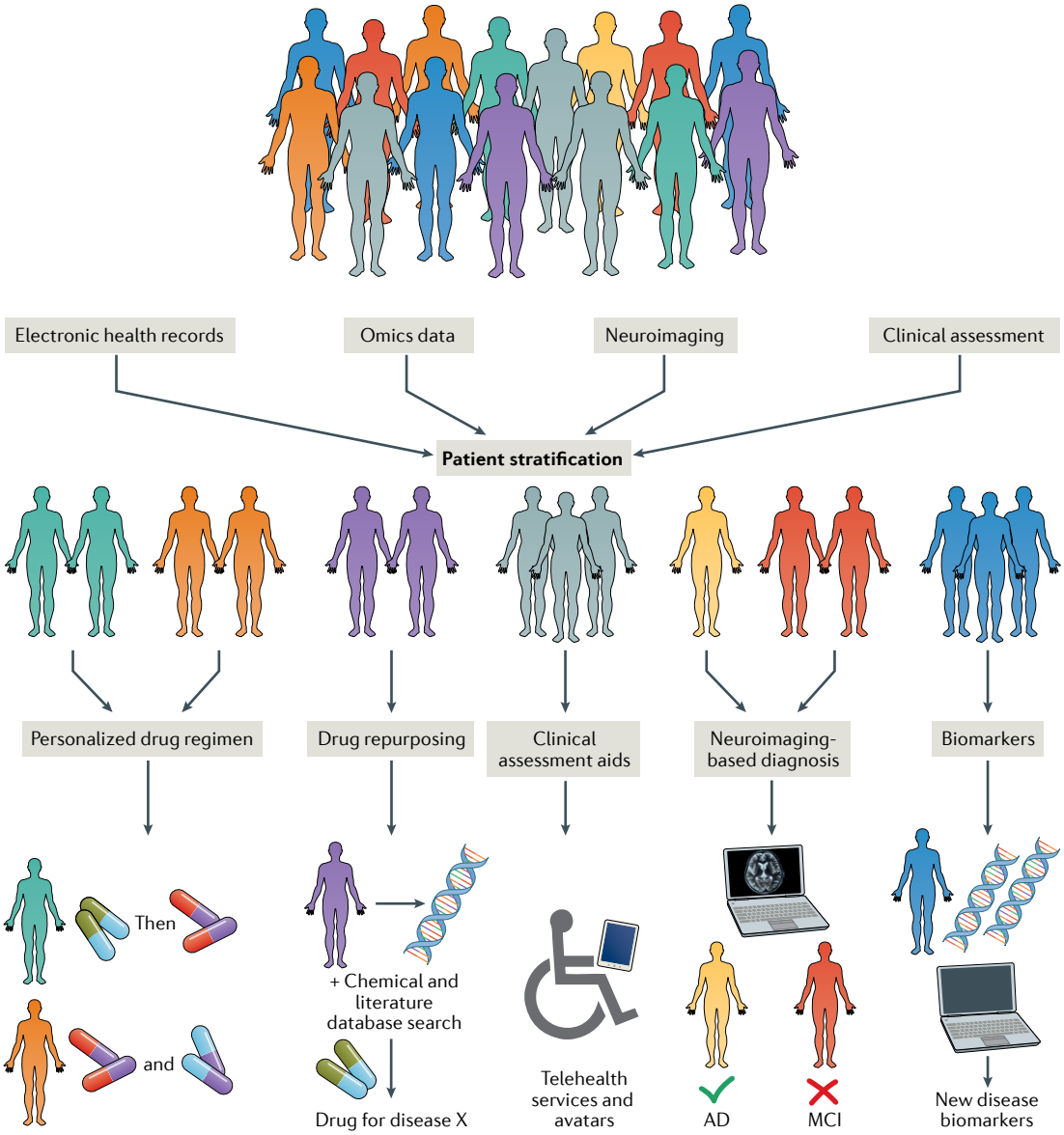

Fig. 4 | **Application of machine learning approaches to development and implementation of treatments for neurodegeneration.** Patient stratification, a process through which a heterogeneous patient population is separated into specific endotypes, helps identify different aetiologies of disease and targets or hallmarks that characterize them. Unsupervised machine learning algorithms can be fed all existing patient information at the point of diagnosis, as well as new information that is gathered as the disease progresses, in order to better understand the underlying disease aetiology. During the course of therapy, any significant event such as adverse reactions, lack of response or cross-reactivity with other medication, can be fed into machine learning algorithms to help build a better understanding of both the disease and the drug, as well as the best therapeutic course of action in each patient. As machine learning algorithms continue to harness the knowledge contained within relevant literature and databases (including chemical and genetic databases), they can help build a comprehensive picture of molecular changes happening in the disease, which can consequently aid identification of new disease targets. This in turn can initiate a new drug discovery cascade, if the target is not yet druggable. Outside the realm of pharmacological treatments, machine learning algorithms could provide therapeutic avatars, for individuals with dementias or could be an indirect point of contact for patients with decreased mobility. Moreover, the field of neurochemical artificial intelligence is focusing on development of novel drugs as well as modifying and/or repurposing existing ones. AD, Alzheimer disease; MCI, mild cognitive impairment. Brain scan image credit: M. Andritoiu/Alamy Stock Photos.

the use of machine learning to aid diagnosis, prognosis and therapeutic development is still in its infancy. In the future, machine learning technologies might enable more precise, earlier diagnosis of neurodegenerative diseases on the basis of medical history, molecular profiles and imaging information, and through the identification of more specific diagnostic biomarkers. More precise diagnosis could be followed by a personalized treatment regimen that will take into consideration the patient's endotype. Machine learning could also reduce the time

and cost involved in performing clinical trials, and increase the likelihood of success, by enabling efficient patient stratification and identifying accurate biomarkers of treatment response. Recent advances in machine learning technology have been made possible by the increased availability of large, multidimensional datasets that are curated by multicentre initiatives, the democratization of machine learning algorithms through open-source code and libraries, and the increased affordability of high-performance computing infrastructures.

Despite the potential of machine learning, creating and applying machine learning algorithms to neurodegenerative disease data remains difficult. One challenge relates to the data itself — machine learning models are only as powerful as the data they rely on. The lack of large datasets, especially multidimensional patient data, for many diseases is a barrier to the application of machine learning. Patient datasets typically consist of only tens or hundreds of patients and tend to be noisy because of measurement inconsistency, error or participant drop-out; these factors all make statistical analyses more prone to errors. Metadata analyses are often necessary because the overlap between results from different datasets can be small. Conducting metadata analyses helps detect, analyse and understand inconsistencies across datasets and increases the statistical power of the data, as the combined dataset now includes more individual cases[189]. Additionally, data are often biased towards certain demographic populations, which limits the generalization of the learning and results in disparity in health care[190].

Data limitations mean that, in practice, most machine learning pipelines start with careful curation of the data, which requires time and expert input. However, new machine learning approaches are being developed to address the problem of small datasets. For example, active learning strategies enable quality inferences from fewer samples than other machine learning methods and remove the need to label large datasets, which can be costly[191]. Active learning methods evaluate and provide feedback on the data as the model is being built, simultaneously making predictions for current datasets and identifying shortcomings in the model by suggesting additional data points to be included. Although active learning has been used in drug design and optimization[192], and could be applied to medical image classification or even patient response profiling, the approach remains largely unexplored with regard to neurodegenerative disease research. In addition, transfer learning is a new method that uses data from one learning task to help in learning another task[193]. For example, a transfer learning algorithm trained to diagnose AD from MRI images, was applied to T2-weighted FLAIR MRI images without a drop in performance[194]. Transfer learning relies on the analysis of a selected subset of data features to reduce data dimensionality, thus avoiding overfitting and making the approach suitable for use on small datasets. Transfer learning has also been used to transfer information on biomarker expression across different neurodegenerative diseases[195], as well as for biomarker discovery from genomic data[196] and diagnosis and classification of individuals with AD from neuroimaging data[197–199]. Special types of generative models, called general adversarial neural networks[200], have been used to generate more training data for learning on biomedical images, for example, by generating MRI images of the brain from images obtained via different imaging platforms such as PET[73]. General adversarial neural networks enable such image manipulation and creation by learning the useful features of the training dataset and generating a new dataset based on the learnt features[201,202].

Robust assessment of machine learning model performance needs to be carried out to select the best model for the task, and to ensure that clinicians can have confidence in the model's output. For well-defined tasks, supervised models can be trained on labelled benchmark data (that is, sources of truth), and the performance of these models can be evaluated by comparing the model output with the benchmark data. However, many other tasks in neurology, such as patient stratification, require unsupervised models that involve no benchmark data, which means that assessing the performance of the model presents a significant challenge. Therefore, evaluation of the performance of unsupervised models uses feedback from experts to establish whether the model output is rational[203], or correlation of the output with other known features such as clinical markers[204]. Even for well-defined tasks, benchmark data are often sparse, meaning that the performance of the model on benchmark data does not necessarily represent the performance of the model on new datasets. This sparsity of benchmark data is especially concerning because some machine learning models are known to be prone to overfitting, which means they become specific to the benchmark data and do not perform well on new datasets. If a machine learning model cannot reliably generalize to new, unseen scenarios, the practical applications are limited. Poor methods of performance evaluation can also lead to over-interpretation of findings and incorrect assumptions about causality.

Another limitation of many machine learning algorithms is that they are 'black boxes', that is, they cannot be used to understand the problem they address or the outputs they produce. Although algorithms are trained using medical knowledge and expertise, explaining exactly why the algorithm performed in a given way is not possible[205,206]. For example, understanding why a deep learning algorithm labelled certain retinal images as showing hallmarks of retinopathy is impossible, even though the predictions might later prove accurate on review by experts[207]. This lack of transparency can severely limit the usefulness of machine learning outputs and therefore the willingness of researchers to adopt these approaches. Fortunately, explainable AI, which aims to build models that can be interpreted and explained, is a growing field[208]. In explainable AI, algorithms trace or rationalize their decision-making in a way that can be understood by humans.

Resolving the challenges involved in applying machine learning to neurodegenerative disease data will require collaboration between experts in biomedicine and machine learning. For example, selecting the right datasets for training and validation, and knowing how

to deal with missing data require a deep understanding of data collection procedures. In order to respond to the pressing demands of developing machine learning systems in a highly complex and often ambiguous space, more cross-disciplinary training programmes are needed. In addition, given the caveats of using and evaluating machine learning technologies, it would be wise to create industry-wide AI assessment and certification tests to ensure that only robust, well-validated technology can impact research or patient care. The widespread integration of machine learning into health-care settings would also pose several practical challenges. For example, implementation of new systems into clinics needs to take into account concerns around job security and career progression of existing health-care personnel, and training needs to be conducted in a way that allows personnel to adapt to the new technology. In a survey of physician perspectives on AI implementation in clinical practice, the commercialization of medical AI systems and the legal, as well as ethical, responsibility of vendors of these systems were amongst the main concerns raised, which highlights the need for appropriate regulatory bodies to be introduced[209].

In conclusion, the integration of machine learning into diagnostic and prognostic neurology practice, as well as the design of future therapeutics, is likely to be achieved with national and international efforts to establish multidisciplinary groups of experts to tackle some of the main challenges discussed in this Review article. The potential of these collaborative efforts is immense when we consider the health challenges our society will have to face in the next 50 years as a result of an increasing ageing population, and the benefits that would result from a faster and more accurate health service.

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Author contributions

L.F. researched data for the article, made a substantial contribution to the discussion of article content, wrote the article, and reviewed and edited the manuscript before submission. M.A.M. researched data for the article, made a substantial contribution to the discussion of article content and wrote the article. P.N.O. and J.D.H. made a substantial contribution to discussion of article content, and reviewed and edited the manuscript before submission. A.M.B.L. and D.N. researched data for the article, and reviewed and edited the manuscript before submission. A.S., R.M. and G.M.H. reviewed and edited the manuscript before submission.

Competing interests

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